Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-12, 14, 15, 17-26, 28, 29, 31-39, 41-48, and 59-68 are pending in the application, with claims 1, 2, and 50 being the independent claims. Claims 13, 16, 27, 30, 40, 49, and 52-58 are sought to be canceled without prejudice or disclaimer to direct the claims to the elected Group **III**, i.e., pyrimidine derivatives. Claims 1-3, 18, 26, 32, 39, 42 and 50 are sought to be amended, and new claims 59-68 are sought to be added. Support for the amendments and new claims 59-68 can be found in the original specification and claims as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested. Specifically, claims 1-3, 18, 26, 32, 39, 42, and 50 have been amended by canceling the non-elected subject matter. In addition, claims 1, 2, and 50 have been amended by replacing the term "alkylthiol" with --alkylthio-- to make the claims more clear as requested by the Examiner.

New claims 59 and 60 are supported by claim 39 as originally filed, and Example 4, paragraphs [0165] through [0169] of the specification as originally filed. New claim 61 is supported by original claim 50. New claims 62 and 63 are supported by originally filed claim 1. New claims 67 and 68 are supported by claim 50 as originally filed. Claims 62 and 67 differ from claim 1 and claim 50, respectively, by not including the term "prodrug". Claims 63 and 68 differ from claim 1 and claim 50, respectively, by not including "amino" as a definition for R_2. Applicants submit that no new matter has been introduced by new claims 62, 63, 67, and 68 since deletion of individual members of Markush expression does not constitute new matter. See, *In re Johnson and Farnham*, 194 U.S.P.Q. 187 (CCPA 1977). New claims 64-66 have support in original claims 3, 18, and 42, respectively.

Applicants reserve the right to file one or more divisional applications directed to the canceled claims 13, 16, 27, 30, 40, 49, and 52-58, and to the subject matter canceled from claims 1-3, 18, 26, 32, 39, 42, and 50.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Restriction/Election of Species Requirement

Applicants note that claims 52-58 are withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a non-elected Group **VI**, and that claims 1-51 are examined to the extent they embrace the elected Group **III**. Applicants are also pleased to note that the elected group is examined using the generic Formula **I** of claim 1.

Rejection under 35 U.S.C. § 112, second paragraph

The present claims 1-38 and 40-51 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

According to the Examiner, the term "prodrug" in claims 1, 2, 17, 31, and 50 is indefinite. Specifically, the Examiner states that

> [p]rodrugs in general and as noted in specification, page 20, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various R, groups include such groups, namely esters, amides, alkoxycaronyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups.

(Office Action, page 3, lines 2-7).

Applicants respectfully disagree. The definitions of the various R groups, other than those mentioned by the Examiner, allow the possibility for the formation of prodrugs. See, for example, the definitions for R_2 including "optionally substituted alkyl, alkenyl or alkynyl", and the definitions for R_3, R_4, R_5, and R_6 including "hydroxyalkyl" and "haloalkyl". A person skilled in the art would know which various R groups defined in claim 1 for Formula **I** would allow the formation of prodrugs and how to prepare them. Applicants respectfully submit that one skilled in the art would be able to ascertain the scope of protection defined by the pending claims with regard to the term "prodrug".

The Examiner states that the recitation of "alkylthiol" in the definitions for R_1 in claims 1, 2, and 50 is indefinite because, according to the Examiner, "alkylthiol" is a class of compounds. Applicants have amended claims 1, 2, and 50 by replacing "alkylthiol" in the definitions for R_1 with --alkylthio-- as suggested by the Examiner.

The Examiner has rejected claims 13, 16, 27, 30, and 40 as reciting a subgenus which is outside the scope of elected Group **III**. Applicants have canceled claims 13, 16, 27, 30, and 40 in favor of divisional prosecution. Applicants have amended claims 1, 2, 3, 18, 26, 32, 42, and 50 accordingly, and also amended claim 39 by canceling pyridyl, pyrazinyl and triazinyl derivatives in favor of divisional prosecution.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of claims 1-38 and 40-51 are respectfully requested.

Rejections under 35 U.S.C. § 102(b)

To anticipate a claim, the reference must teach each and every element of the claim. M.P.E.P. § 2131.

I Kim et al. (U.S. Pat. No. 3,631,036)

Claims 1 and 50-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Kim *et al.* (U.S. Pat. No. 3,631,036). Applicants respectfully traverse this rejection.

The Examiner asserts as follows:

> Kim et al. teaches several pyrimidine compounds, which include those claimed in the instant claims generically, for use as CNS depressants (sedative effect). See formula I on col. 1 and note the definition of various variable R groups. Note the compound disclosed meet instant R_1 and R_2 taken together form a heterocyclic ring requirement. See col. 2-6 for the process of making them and example 1-13 on col. 4- through 18 for compounds made note various intermediate pyrimidines are also disclosed on col. 7-10.

(Office Action, page 4, lines 3-9).

Applicants respectfully disagree. R^1 in formula I of Kim *et al.* corresponds to the optionally substituted Y-X-phenyl- group of Formula **I** of the present invention. Kim *et al.* define in column 1 the substituent R^1 as "lower alkyl, phenyl, halophenyl, lower alkylphenyl, lower alkoxyphenyl, or lower alkylthio." None of these substituents is an optionally substituted phenyl-X-phenyl group attached to a pyrimidine ring as claimed in claims 1 and 50 of the present application. Compounds of formula I of Kim *et al.* include lower alkylphenyl and lower alkoxyphenyl as substituent R^1. However, in this situation, claims 1 and 50 of the present application require that R_1 is aminocarbonyl. None of the compounds of formula I of Kim *et al.* fulfil this requirement. The above applies also to the intermediate pyrimidines purportedly described on col. 2-6 and in examples 1-13 of Kim *et al.* It is respectfully submitted that Kim *et al.* does not disclose any compound that falls into the scope of claim 1. Furthermore, Kim *et al.* does not disclose any pharmaceutical composition encompassed by claims 50 or 51. Kim *et al.* do not teach each and every aspect of claims 1, 50, and 51 and, therefore, claims 1, 50 or 51, or any claim dependent on any of those claims, are not anticipated by Kim *et al.*

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 1 and 50-51 are respectfully requested.

II Tsumotu et al. (GB 2,095,240)

Claims 1 and 50-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Tsumotu *et al.* (GB 2,095,240). Applicants respectfully traverse this rejection.

The Examiner states that

> Tsumotu et al. teaches several pyrimidine compounds, which include those claimed in the instant claims generically, for use as anti-allergic agents. See page 1, formula I and note the definition of R_1 includes (un)substituted aryl. Note the process for making it. Particularly note, Tsumotu et al teaches the intermediate compound of formula II which is also embraced in the instant claims. See page 2 for details of the process and pages 3-13 for compounds made.

(Office Action, page 4, lines 12-17).

Applicants respectfully disagree. It is respectfully submitted that Tsumotu *et al.* do not describe any compound or pharmaceutical composition that falls into the scope of claims 1 or 50, respectively. Compounds of Tsumotu *et al.* require a "6-oxo" substituent in the pyrimidine ring as shown in formula I and formula II. In Formula **I** of the present invention, the position of A_2 corresponds to the "6-oxo" substituent of Tsumotu *et al.* Claims 1 and 50 of the present invention define A_2 as CR_2, wherein "R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino." Neither claim 1 nor claim 50 of the present invention define R_2 as "oxo". Thus, Tsumotu *et al.* do not teach each and every element of claims 1, 50, and 51 and, therefore, Tsumotu *et al.* do not anticipate claims 1, 50 or 51 or any claim dependent on these claims.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 1 and 50-51 are respectfully requested.

III Hepworth et al. (U.S. Pat. No. 3,502,673)

Claims 1 and 50-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hepworth *et al.* (U.S. Pat. No. 3,502,673). Applicants respectfully traverse this rejection.

The Examiner asserts as follows:

> Hepworth et al. teaches several pyrimidine compounds, which include those claimed in the instant claims generically, for use analgesics, anti-inflammatory and antipyritic agents. See formula I on col. 1 and note the definition of various W, X, Y and Z groups. Note especially the definition of Z includes alkoxycarbonylalkyl or amido carbonylalkyl which meets instant R_1 definition of optionally substituted alkyl. See col. 2-9 for preferred embodiments and the process of making them and example 1-54 on col. 10 through 25 for compounds made.

(Office Action, page 4, line 3 from the bottom of the page through page 5, line 4).

Applicants respectfully disagree. It is respectfully submitted that Hepworth *et al.* do not describe any compound or pharmaceutical composition that falls into the scope of claims 1 or 50, respectively. None of the definitions for W, X, Y, and Z groups in the formula of Hepworth *et al.* include an optionally substituted phenyl-X-phenyl group attached to a pyrimidine ring as claimed in claims 1 and 50 of the present application. Compounds of the formula of Hepworth *et al.* include a phenyl radical optionally substituted with trifluoromethyl as the substituent Y. However, in this situation, claims 1 and 50 of the present application require that R_1 is aminocarbonyl. Hepworth *et al.* does not define any of the substituents W, X, or Z as aminocarbonyl. The above applies also to the preferred embodiments and compounds made in examples 1-54 of Hepworth *et al.* Thus, Hepworth *et al.* do not teach each and every aspect of claims 1, 50 and 51 and, therefore, claims 1, 50 or 51, or any claim dependent on any of those claims, are not anticipated by Hepworth *et al.*

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 1 and 50-51 are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious, but whether the claimed invention *as a whole* would have been obvious. *See* M.P.E.P. § 2141.02. Thus, a prior art reference must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 861 (1984).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *See* M.P.E.P. § 2143.

I Rorig et al. (U.S. Pat No. 3,149,109)

Claims 1 and 50-51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rorig *et al.* (U.S. Pat No. 3,149,109). Applicants respectfully traverse this rejection.

The Examiner alleges that

> Rorig et al. teaches several pyrimidine compounds, which include those claimed in the instant claims generically, for use antibiotics and anti-inflammatory. See formula I on col. 1 and note the definition of Ar, R and X. Note when Ar is para tolyl group, the compounds taught by Rorig *et al*

> includes those claimed in the instant claims. See example 3 and 6 on col. 3 and col. 4, which show compounds with unsubstituted phenyl ring.

(Office Action, page 5, lines 6-11 from the bottom of the page).

The Examiner continues as follows:

> [i]nstant claims require a methyl substituent in para position of the phenyl ring. However, Rorig et al. teaches the equivalency exemplified substituted phenyl ring with para tolyl group claimed therein. See col. 1. line25-26. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in the aryl ring as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

(Office Action, page 5, line 5 from the bottom of the page through page 6, line 2).

Applicants respectfully disagree. Applicants respectfully submit that the Examiner has failed to establish *prima facie* case of obviousness. In particular, Rorig *et al.* do not teach or suggest all the claim limitations. Claims 1 and 50 of the present application require that when R_7 is an optionally substituted alkyl, R_1 is an aminocarbonyl group. Rorig *et al.* do not teach or suggest that when Ar is p-tolyl, X or R is aminocarbonyl. It is respectfully submitted that there is no suggestion or motivation in Rorig *et al.* for one of ordinary skill in the art to prepare the compounds or pharmaceutical compositions of the present invention with a reasonable expectation of success.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 1 and 50-51 are respectfully requested.

II El-Kafrawy et al. (J. Chem. Soc. Pak. 14(1):59-66 (1992))

Claims 1-3, 6, 8-11, 14-15, 17-19, 21-25, and 50-51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over El-Kafrawy *et al.* (*J. Chem. Soc. Pak. 14(1)*:59-66 (1992)). Applicants respectfully traverse this rejection.

The Examiner refers to page 63 of the reference, compounds 4a through 4c, 5a, and 5b, and alleges as follows:

> [i]nstant compounds require a carboxyl group at 2 or 4 position for R_1 and an amino at other available position for R_2. While said compound(s) doesn't anticipate the scope of instant claims, they are very closely related, being positional isomers of compounds i.e. 2-carboxyl and 6-amino of instant R_1 vs 2-amino and 6-carboxyl in the pyrimidine ring of the reference. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. . . . Thus it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

(Office Action, page 6, lines 9-20).

Applicants respectfully disagree. Applicants respectfully submit that the Examiner has failed to establish *prima facie* case of obviousness. In particular, El-Kafrawy *et al.* do not teach or suggest all the claim limitations and, furthermore, teach away from the present invention.

Compounds 4a-4h, including compounds 4a-4c, of El-Kafrawy *et al.* do not include a pyrimidine ring as required by the claims of the present invention as amended, but a partially hydrogenated pyrimidine ring. Further, compounds 4a-4c include a hydrazino group. Neither of the substituents R_1 and R_2 in the present claims are defined as hydrazino or any other group taught by compounds 4d-4h. Thus, compounds 4a-4c do not teach or suggest all the claim limitations.

Compounds 5a and 5b on page 63 of El-Kafrawy *et al.* are not positional isomers of compounds of the present invention having a 2-carboxy group and a 6-amino group because the structures of compounds 5a and 5b as taught on page 63 do not include a pyrimidine ring but a partially hydrogenated pyrimidine ring. However, Applicants note that the molecular formulae and molecular weights described for compounds 5a and 5b in Table 1, at page 61 of El-Kafrawy *et al.*, could indicate that compounds 5a and 5b have a pyrimidine ring. It should also be noted that there are many organic compounds

having the molecular formulae the same as those taught for compounds 5a and 5b in Table 1 that do not have a pyrimidine ring. Therefore, it is respectfully submitted that the teaching of El-Kafrawy *et al.* would have been ambiguous for a person skilled in the art at the time the present invention was made with regard to compounds 5a and 5b.

Even if compounds 5a and 5b were pyrimidine compounds having 2-amino and 6-carboxy substituents in the pyrimidine rings, they teach away from the compounds of the present invention. Specifically, El-Kafrawy *et al.* teach in Table 2, at page 62, that compound 5a is less effective as an antimicrobial compound than compound 5b. Table 2 shows that compound 5a exhibits an antimicrobial activity against only *one* of the three tested bacteria, namely *Bacillus pumilus*, and the inhibition zone (I.Z.) for compound 5a is only 57 % of that of the standard antibiotic Neomycin and 53 % of that of compound 5b. Table 2 shows that compound 5b exhibits an antimicrobial activity against *two* of the three tested bacteria, namely, *Bacillus pumilus* and *Micrococcus luteus*. In fact, compound 5b shows the highest activity against *Bacillus pumilus* than any of the tested compounds, even higher than that of the standard antibiotic Neomycin. It is respectfully submitted that the test results for compounds 5a and 5b presented in Table 2 would suggest a person skilled in the art to modify compound 5b rather than 5a in order to prepare effective antimicrobial compounds. Thus, El-Kafrawy *et al.* teach away from compounds structurally similar to compound 5a. The structural difference between compounds 5a and 5b is that compound 5a includes a phenyl-O-phenyl group attached to the alleged pyrimidine ring and in compound 5b the phenyl-O-phenyl group is replaced with a 3,4-dichlorophenyl group. Therefore, it is respectfully submitted that there is no teaching or suggestion in El-Kafrawy *et al.* for a person skilled in the art at the time of the invention was made to prepare pyrimidine compounds of Formula **I** of the present invention wherein R_1 is carboxy, R_2 is amino, and Y is an optionally substituted phenyl with a reasonable expectation of success.

As stated above, compound 5b of El-Kafrawy *et al.* includes a 3,4-dichlorophenyl group attached to the alleged pyrimidine ring. The 4-Cl substituent in compound 5b

corresponds to the substituent Y-X- of Formula **I** of the present invention where X is absent, i.e., the 4-Cl-substituent corresponds to R_7 of Formula **I** of the present invention. However, R_7 is defined as "optionally substituted alkyl" in claim 1 of the present invention. Further, claim 1 requires that when Y is R_7 then R_1 is aminocarbonyl. This is neither taught nor suggested by El-Kafrawy *et al.* Thus, El-Kafrawy *et al.* do not teach or suggest all the claim limitations. It is respectfully submitted that there is no teaching or suggestion in El-Kafrawy *et al.* for a person skilled in the art to modify compound 5b in a way to reach compounds of Formula **I** of the present invention where Y is R_7 with a reasonable expectation of success.

In view of the above, it is respectfully submitted that there is no suggestion or motivation in El-Kafrawy *et al.* for one of ordinary skill in the art to prepare the compounds or pharmaceutical compositions of the present invention with a reasonable expectation of success and, therefore, it would not have been obvious to one skilled in the art at the time the invention was made to expect instant compounds to possess the utility taught by El-Kafrawy *et al.*

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 1-3, 6, 8-11, 14-15, 17-19, 21-25, and 50-51 are respectfully requested.

III Terada et al. (U.S. Pat. No. 5,405,553)

Claims 1 and 50-51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Terada *et al.* (U.S. Pat No. 5,405,553). Applicants respectfully traverse this rejection.

The Examiner refers to formula I-f at column 9 and examples I-18 through I-21, and asserts as follows:

> [i]nstant compounds require an alkoxycarbonyl group at 2 or 4 position for R_1. While said compound(s) doesn't anticipate the scope of the instant claims, they are very closely related, being positional isomers of compounds i.e. 2-alkoxycarbonyl or 5-alkoxycarbonyl of instant R_1 vs 5-

> alkoxycarbonyl of the reference in the pyrimidine ring. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. . . . Thus it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

(Office Action, page 7, lines 4-14).

Applicants respectfully disagree. Applicants respectfully submit that the Examiner has failed to establish *prima facie* case of obviousness. In particular, Terada *et al.* do not teach or suggest all the claim limitations. Compounds of the present invention and compounds of Terada *et al.* are not positional isomers. Claims 1 and 50 of the present application require that when R_7 is an optionally substituted alkyl, R_1 is an aminocarbonyl group. Formula I-f at column 9 of Terada *et al.* describes a pyrimidine derivative where R_2, that corresponds to R_7 of the present invention, is a branched alkyl group. Examples I-18 through I-21 of Terada *et al.* teach pyrimidine derivatives wherein the group corresponding to R_7 of the present invention is a branched alkyl group. However, the group attached to the pyrimidine ring in the compounds I-f and I-18 through I-21 of Terada *et al.* is an alkoxycarbonyl group instead of an aminocarbonyl group. Terada *et al.* does not teach or suggest an aminocarbonyl substituent in the pyrimidine ring. It is respectfully submitted that there is no suggestion or motivation in Terada *et al.* for one of ordinary skill in the art to prepare the compounds or pharmaceutical compositions of the present invention with a reasonable expectation of success and, therefore, it would not have been obvious to one skilled in the art at the time the invention was made to expect instant compounds to possess the utility taught by Terada *et al.*

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 1 and 50-51 are respectfully requested.

Objections and Allowable Subject Matter

The Examiner has objected to claim 39 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants respectfully traverse this objection. In view of the above arguments, Applicants submit that the rejections have been rendered moot and that the claims are patentable in view of the references cited by the Examiner. Applicants have amended claim 39 to direct it to the subject matter of the elected Group **III**. Reconsideration and withdrawal of the objection to claim 39 are respectfully requested.

Applicants note with appreciation that the Examiner has found claim 39 allowable since specific species embraced in this claim are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
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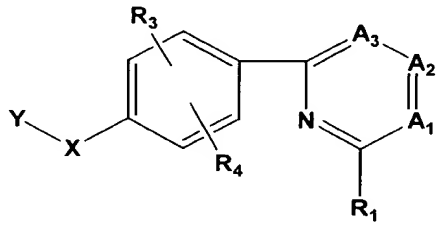
Version with markings to show changes made

Claims 13, 16, 27, 30, 40, 49, and 52-58 have been canceled.

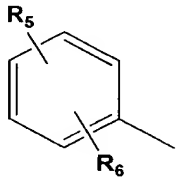
New claims 59-68 have been added.

Claims 1-3, 18, 26, 32, 39, 42, and 50 have been amended as follows:

1. (Once Amended) A compound having the Formula **I**:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is 

or R_7,

provided that when Y is R_7, R_1 is aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2 [A_1, A_2 and A_3 are independently CR_2 or N, provided that A_1, A_2 and A_3 are not all N at the same time];

R_1 is selected from the group consisting an optionally substituted alkyl, amino, [alkylthiol] alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy,

azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

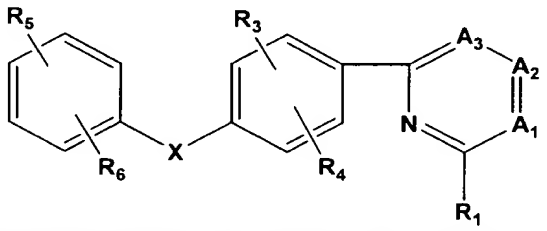
X is one of O, S, NH, or CH_2 when Y is other than R_7; or

X is one of O, S, NH, CH_2 or absent when Y is R_7;

with the [provisos] proviso that[:

1)]R_2 is not methoxy if R_5 is trifluoromethyl, R_6 is H, X is O and R_1 is SO_2CH_2Ph[;
2) R_2 is not NH_2 if R_1 is methylthio, X is O and two of A_1, A_2 and A_3 are N;
3) R_2 is not methyl if R_1 is SO_2R_8, wherein R_8 is methylphenyl, R_3 and R_4 are methoxy, X is S and two of A_1, A_2 and A_3 are N;
4) R_2 is not CCl_3 if R_1 is CCl_3, X is S and two of A_1, A_2 and A_3 are N; or
5) R_1 and R_2 are not both NH_2 if X is O or S and two of A_1, A_2 and A_3 are N].

2. (Once Amended) A compound having the Formula **II**:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2 [A_1, A_2 and A_3 are independently CR_2 or N, provided that A_1, A_2 and A_3 are not all N at the same time];

R_1 is selected from the group consisting an optionally substituted alkyl, amino, [alkylthiol] alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-

pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2;

with the [provisos] proviso that[:

1)]R_2 is not methoxy if R_5 is trifluoromethyl, R_6 is H, X is O and R_1 is SO_2CH_2Ph[;
2) R_2 is not NH_2 if R_1 is methylthio, X is O and two of A_1, A_2 and A_3 are N;
3) R_2 is not methyl if R_1 is SO_2R_8, wherein R_8 is methylphenyl, R_3 and R_4 are methoxy, X is S and two of A_1, A_2 and A_3 are N;
4) R_2 is not CCl_3 if R_1 is CCl_3, X is S and two of A_1, A_2 and A_3 are N; or
5) R_1 and R_2 are not both NH_2 if X is O or S and two of A_1, A_2 and A_3 are N].

3. (Once Amended) The compound of claim 2, wherein [A_1, A_2 and A_3 are each CR_2; or A_1 is N and A_2 and A_3 are CR_2; or] A_3 is N and A_1 and A_2 are CR_2[; or A_2 is N and A_1 and A_3 are CR_2; or A_1 and A_3 are N and A_2 is CR_2].

18. (Once Amended) The compound of claim 17, wherein [A_1, A_2 and A_3 are each CR_2; or A_1 is N and A_2 and A_3 are CR_2; or] A_3 is N and A_1 and A_2 are CR_2[; or A_2 is N and A_1 and A_3 are CR_2; or A_1 and A_3 are N and A_2 is CR_2].

26. (Once Amended) The compound of claim 17, wherein

X is O;

[A_1, A_2 and A_3 are each CR_2; or] A_1 is N and A_2 and A_3 are CR_2; or A_3 is N and A_1 and A_2 are CR_2[; or A_2 is N and A_1 and A_3 are CR_2; or A_1 and A_3 are N and A_2 is CR_2]; wherein

R_2 is selected from the group consisting of hydrogen, alkyl, alkoxy, aminoalkyl, and aminocarbonyl;

R_3 and R_4 are both hydrogen;

R_5 and R_6 are independently selected from the group consisting of hydrogen, alkyl, halogen, haloalkyl, and nitro; and

R_8 is amino.

32. (Once Amended) The compound of claim 31, wherein [A_1, A_2 and A_3 are each CR_2; or A_1 is N and A_2 and A_3 are CR_2; or A_3 is N and A_1 and A_2 are CR_2; or A_2 is N and A_1 and A_3 are CR_2; or A_1 and A_3 are N and A_2 is CR_2, and] R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aminoalkyl, amino, hydroxyalkyl, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino.

39. (Once Amended) A compound of claim 2, wherein said compound is:

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(4-nitrophenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(4-methoxyphenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(4-trifluoromethylphenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(3-chloro-2-cyanophenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(2,4-difluorophenoxy)phenyl]pyrimidine-2-carboxamide;

4-[4-(2-chloro-4-fluorophenoxy)phenyl]pyrimidine-2-carboxamide;

1-[4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-yl]-ethanone;

2-[4-(4-fluorophenoxy)phenyl]pyrimidine-4-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-4-methylpyrimidine;

2-methyl-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid sodium salt;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid methylamide;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid dimethylamide;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid *tert*-butylamide;

2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide;

2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxylic acid;

2-(4-phenoxyphenyl)-6-(dimethylamino)pyrimidine-4-carboxylic acid dimethylamide;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid 2-hydroxyethylamide;

4-[4-(4-fluorophenoxy)phenyl]pyrimidine-2-carboxylic acid hydroxymethyleneamide;

2-(2-hydroxyprop-2-yl)-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

4-[4-(2,4-difluorophenoxy)phenyl]pyrimidine-2-carboxylic acid 2-morpholin-4-yl-ethyl amide;

2-(4,5-dihydro-1H-imidazol-2-yl)-4-[4-(4-fluorophenoxy)phenyl]-pyrimidine;

2-(3-pyrazolyl)-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

2-(5-isoxazolyl)-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

2-(1-methyl-3-pyrazolyl)-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxylic acid methylamide;

3-dimethylamino-1-{4-[4-(4-fluorophenoxy)phenyl}pyrimidin-2-yl]propenone;

2-thiomethyl-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

2-methanesulfonyl-4-[4-(4-fluorophenoxy)phenyl]pyrimidine;

2-[4-(4-chloro-2-fluorophenoxy)phenyl]-4-methyl-pyrimidine;

4-[4-(4-fluorophenoxy)-3-fluorophenyl]pyrimidine-2-carboxamide; or

2-[4-(4-fluorophenoxy)-3-fluorophenyl]pyrimidine-4-carboxamide;

[2-methyl-6-(4-phenoxyphenyl)pyridine;

6-(4-phenoxyphenyl)pyridine-2-carboxamide;

2-methyl-6-[4-(4-fluorophenoxy)phenyl]pyridine;

6-(4-phenoxyphenyl)pyridine-2-carboxylic acid;

6-(4-phenoxyphenyl)pyridine-2-carboxylic acid methylamide;

6-[4-(4-fluorophenoxy)phenyl]pyridine-2-carboxamide;

6-[4-(2,4-difluorophenoxy)phenyl]pyridine-2-carboxamide;

6-[4-(4-chloro-2-fluorophenoxy)phenyl]pyridine-2-carboxamide;

6-[4-(4-fluorophenoxy)-3-fluorophenyl]pyridine-2-carboxamide;

6-[4-(4-trifluoromethylphenoxy)phenyl]pyridine-2-carboxamide;

6-(4-phenoxyphenyl)pyrazine-2-carboxamide;

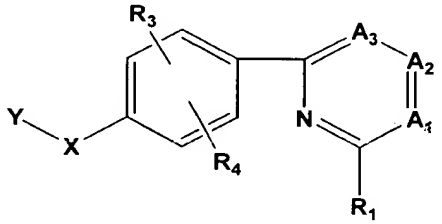
3,5-diamino-6-(4-phenoxyphenyl)pyrazine-2-carboxamide; or

2-[4-(4-nitrophenoxy)phenyl]-4-methyl-[1,3,5]-triazine,]

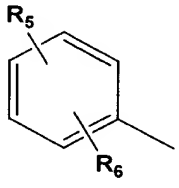
or a pharmaceutically acceptable salt, prodrug or solvate thereof.

42. (Once Amended) The compound of claim 41, wherein [A_1, A_2 and A_3 are each CR_2; or A_1 is N and A_2 and A_3 are CR_2; or] A_3 is N and A_1 and A_2 are CR_2[; or A_2 is N and A_1 and A_3 are CR_2; or A_1 and A_3 are N and A_2 is CR_2].

50. (Once Amended) A pharmaceutical composition, comprising the compound of formula:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is 

or R_7, provided that when Y is R_7, R_1 is aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2 [A_1, A_2 and A_3 are independently CR_2 or N, provided that A_1, A_2 and A_3 are not all N at the same time];

R_1 is selected from the group consisting an optionally substituted alkyl, amino, [alkylthiol] alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Y is other than R_7; or

X is one of O, S, NH, CH_2 or absent when Y is R_7; and a pharmaceutically acceptable carrier or diluent.